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(30) 1997/10/16 (08/951,733) US

(54) **GENES CODANT DES PROTEINES DE TELOMERASE**

(54) **GENES ENCODING TELOMERASE PROTEINS**

(57) L'invention concerne des molécules d'acide nucléique, qui codent des polypeptides du complexe télomérase. L'invention se rapporte également à des procédés de préparation desdites molécules d'acide nucléique et desdits polypeptides et à des procédés d'utilisation desdites molécules.

(57) Disclosed are nucleic acid molecules encoding polypeptides of the telomerase complex. Also disclosed are methods of preparing the nucleic acid molecules and polypeptides, and methods of using these molecules.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/21248 (22) International Filing Date: 13 November 1997 (13.11.97) (30) Priority Data: 08/871,189 15 November 1996 (15.11.96) US 08/873,039 11 June 1997 (11.06.97) US 08/951,733 16 October 1997 (16.10.97) US (71) Applicants: AMGEN INC. [US/US]; Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US). AMGEN CANADA INC. [CA/CA]; Suite 303, 6733 Mississauga Road, Mississauga, Ontario L5N 6J5 (CA). (72) Inventors: HARRINGTON, Lea, A.; 55 Pears Avenue, Toronto, Ontario M5R 1S9 (CA). ROBINSON, Murray, O.; 22623 Pacific Coast Highway, Malibu, CA 90265 (US). (74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., Amgen Center, 1840 De Havilland Drive, Thousand Oaks, CA 91320-1789 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BF BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NC NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GF KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ BY, KG, KZ, MD, RU, TJ, TM) European patent (AT, BE CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NI PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>With amended claims and statement.</i> Date of publication of the amended claims and statement: 30 July 1998 (30.07.98)
(54) Title: GENES ENCODING TELOMERASE PROTEINS (57) Abstract Disclosed are nucleic acid molecules encoding polypeptides of the telomerase complex. Also disclosed are methods of preparing the nucleic acid molecules and polypeptides, and methods of using these molecules.		

WO 98/21343

PCT/US97/21248

- 103 -

AMENDED CLAIMS

[received by the International Bureau on 19 June 1998 (19.06.98);
new claims 33-56 added; remaining claims unchanged (7 pages)]

1. A TP2 nucleic acid molecule encoding a polypeptide selected from the group consisting of:

5 (a) the nucleic acid molecule of SEQ ID NO:13;

(b) the nucleic acid molecule that is nucleotides 1920-2820 of SEQ ID NO:13;

(c) the nucleic acid molecule of SEQ ID NO:19

10 (d) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:14, or a biologically active fragment thereof;

(e) a nucleic acid molecule encoding the polypeptide of SEQ ID NO:20, or a biologically active
15 fragment thereof;

(f) a nucleic acid molecule that encodes a polypeptide that is at least 90 percent identical to the polypeptide of SEQ ID NO:14;

20 (g) a nucleic acid molecule that encodes a polypeptide that is at least 90 percent identical to the polypeptide of SEQ ID NO:20;

(h) a nucleic acid molecule that hybridizes under stringent conditions to any of (a)-(g) above; and

25 (i) a nucleic acid molecule that is the complement of any of (a)-(g) above.

2. The nucleic acid molecule that is SEQ ID NO:13 or SEQ ID NO:19.

30 3. The nucleic acid molecule that is nucleotides 1920-2820 of SEQ ID NO:13.

4. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:14 of SEQ ID NO:20.

35

AMENDED SHEET (ARTICLE 19)

WO 98/21343

PCT/US97/21248

- 104 -

5. A nucleic acid molecule selected from the group consisting of: nucleotides 1-1689 of SEQ ID NO:13, nucleotides 1-1920 of SEQ ID NO:13, nucleotides 1920-2820 of SEQ ID NO:13, nucleotides 2089-2820 of SEQ ID NO:13, and nucleotides 2089-2859 of SEQ ID NO:13.
6. A nucleic acid molecule encoding amino acids 640-940 of the polypeptide of SEQ ID NO:14.
7. A vector comprising the nucleic acid molecule of claim 1.
8. A vector comprising the nucleic acid molecule of claim 2.
9. A vector comprising the nucleic acid molecule of claim 3.
10. A vector comprising the nucleic acid molecule of claim 4.
11. A vector comprising the nucleic acid molecule of claim 5.
12. A vector comprising the nucleic acid molecule of claim 6.
13. A host cell comprising the vector of claim 7.
14. A host cell comprising the vector of claim 8.
15. A host cell comprising the vector of claim 9.

AMENDED SHEET (ARTICLE 19)

WO 98/21343

PCT/US97/21248

- 105 -

16. A host cell comprising the vector of
claim 10.

5 17. A host cell comprising the vector of
claim 11.

18. A host cell comprising the vector of
claim 12.

10 19. A process for producing a TP2 polypeptide
comprising the steps of:

(a) expressing a polypeptide encoded by the
nucleic acid of claim 1 in a suitable host; and
15 (b) isolating the polypeptide.

20. The process of claim 19 wherein the
polypeptide is SEQ ID NO:14 or SEQ ID NO:20.

20 21. The process of claim 19 wherein the
polypeptide is amino acids 640-940 of SEQ ID NO:14.

22. A TP2 polypeptide selected from the group
consisting of:

25 (a) the polypeptide of SEQ ID NO:14;
(b) the polypeptide that is amino acids 640-
940 of SEQ ID NO:14;
(c) the polypeptide of SEQ ID NO:20; and
(d) a polypeptide that is at least 90 percent
30 identical to any of the polypeptides of (a)-(c).

23. A TP2 polypeptide that is the polypeptide
of SEQ ID NO:14, SEQ ID NO:20, or a biologically active
fragment thereof.

35

AMENDED SHEET (ARTICLE 19)

WO 98/21343

PCT/US97/21248

- 106 -

24. A TP2 polypeptide selected from the group consisting of: amino acids 1-563 of SEQ ID NO:14; amino acids 1-640 of SEQ ID NO:14; amino acids 640-940 of SEQ ID NO:14; amino acids 696-940 of SEQ ID NO:14; and
5 amino acids 696-953 of SEQ ID NO:14.

25. The TP2 polypeptide of claim 22 that does not possess an amino terminal methionine.

10 26. A method of increasing proliferation of a cell, comprising expressing a nucleic acid encoding TP2 or a biologically active fragment thereof, in the cell.

15 27. A method of increasing telomerase activity in a cell, comprising expressing a TP2 gene, or a biologically active fragment thereof, in the cell.

20 28. A method of decreasing telomerase in a cell, comprising expressing a TP2 mutant in a cell, wherein the mutant does not have TP2 biological activity.

25 29. A nucleic acid molecule encoding a mutant TP2 polypeptide, wherein the codon for aspartic acid at amino acid position 868 or 869 is changed to a codon for alanine.

30 30. A nucleic acid molecule encoding a mutant TP2 polypeptide, wherein the codons for aspartic acid at amino acid positions 868 and 869 are changed to codons for alanine.

35 31. A polypeptide encoded by the nucleic acid molecule of claim 29.

32. A polypeptide encoded by the nucleic acid molecule of claim 30.

5 33. A TRIP1 nucleic acid molecule encoding a polypeptide selected from the group consisting of:

 (a) the nucleic acid molecule of SEQ ID NO:1;
 (b) the nucleic acid molecule of SEQ ID NO:2;
 (c) a nucleic acid molecule encoding the
10 polypeptide of SEQ ID NO:3, SEQ ID NO:4, or a biologically active fragment thereof;

 (d) a nucleic acid molecule that encodes a polypeptide that is at least 70 percent identical to the polypeptide of SEQ ID NO:3 or SEQ ID NO:4;

15 (e) a nucleic acid molecule that hybridizes under stringent conditions to any of (a)-(d) above; and
 (f) a nucleic acid molecule that is the complement of any of (a)-(e) above.

20 34. The nucleic acid molecule that is SEQ ID NO:1.

 35. The nucleic acid molecule that is SEQ ID NO:2.

25 36. A nucleic acid molecule encoding the polypeptide of SEQ ID NO:3.

 37. A nucleic acid molecule encoding the
30 polypeptide of SEQ ID NO:4.

 38. A nucleic acid molecule encoding amino acids 1-871 of the polypeptide of SEQ ID NO:3.

39. A vector comprising the nucleic acid molecule of claim 33.

40. A vector comprising the nucleic acid molecule of claim 34.

41. A vector comprising the nucleic acid molecule of claim 35.

42. A vector comprising the nucleic acid molecule of claim 36.

43. A vector comprising the nucleic acid molecule of claim 37.

44. A vector comprising the nucleic acid molecule of claim 38.

45. A host cell comprising the vector of claim 39.

46. A host cell comprising the vector of claim 40.

47. A host cell comprising the vector of claim 41.

48. A host cell comprising the vector of claim 42.

49. A host cell comprising the vector of claim 43.

50. A host cell comprising the vector of claim 44.

51. A process for producing a TRIP1 polypeptide comprising the steps of:

- 5 (a) expressing a polypeptide encoded by the nucleic acid of claim 1 in a suitable host; and
(b) isolating the polypeptide.

52. The process of claim 51 wherein the polypeptide is SEQ ID NO:3.

10

53. The process of claim 51 wherein the polypeptide amino acids 1-871 of SEQ ID NO:3.

54. A TRIP1 polypeptide selected from the group consisting of:

- 15 (a) the polypeptide of SEQ ID NO:3;
(b) the polypeptide that is amino acids 1-871 of SEQ ID NO:3; and
(c) a polypeptide that is at least 70 percent
20 identical to the polypeptide of (a) or (b).

55. A TRIP1 polypeptide that is the polypeptide of SEQ ID NO:3 or a biologically active fragment thereof.

25

56. The TRIP1 polypeptide of claim 52 that does not possess an amino terminal methionine.

STATEMENT UNDER ARTICLE 19

The claims of International Application WO 98/21248, published 22 May 1998, have been amended. Original claims 1 through 32 have not been amended, however, new claims 33 through 56 have been added. Claims 33 through 56 are directed to an aspect of the invention not originally claimed by Applicants. Specifically, claims 33 through 56 encompass telomerase protein 1 and DNA encoding therefor. Such claims are fully supported by the written description and the drawings.

1 / 4 6

FIG. 1A

ATGGAAAACTCCATGGGCATGTGTCTGCCCATCCAGACATCCTCTCCT
TGGAGAACCGGTGCCTGGCTATGCTCCCTGACTTACAGCCCTTGGAGAA
ACTACATCAGCATGTATCTACCCACTCAGATATCCTCTCCTTGAAGAAC
CAGTGCCTAGCCACGCTTCCTGACCTGAAGACCATGGAAAAACCACATG
GATATGTGTCTGCCCACCCAGACATCCTCTCCTTGGAGAACCAGTGCCT
GGCCACACTTTCTGACCTGAAGACCATGGAGAAACCACATGGACATGTT
TCTGCCCACCCAGACATCCTCTCCTTGGAGAACCGGTGCCTGGCCACCC
TCCCTAGTCTAAAGAGCACTGTGTCTGCCAGCCCCTTGTTCCAGAGTCT
ACAGATATCTCACATGACGCAAGCTGATTTGTACCGTGTGAACAACAGC
AATTGCCTGCTCTCTGAGCCTCCAAGTTGGAGGGCTCAGCATTTCTCTA
AGGGACTAGACCTTTCAACCTGCCCTATAGCCCTGAAATCCATCTCTGC
CACAGAGACAGCTCAGGAAGCAACTTTGGGTCGTTGGTTTGATTCAGAA
GAGAAGAAAGGGGCAGAGACCCAAATGCCTTCTTATAGTCTGAGCTTGG
GAGAGGAGGAGGAGGTGGAGGATCTGGCCGTGAAGCTCACCTCTGGAGA
CTCTGAATCTCATCCAGAGCCTACTGACCATGTCCTTCAGGAAAAGAAG
ATGGCTCTACTGAGCTTGCTGTGCTCTACTCTGGTCTCAGAAGTAAACA
TGAACAATACATCTGACCCCAACCCTGGCTGCCATTTTTTGAAATCTGTCTG
TGAACCTGCCCTCCTGGAGCCTGAGTTTATCCTCAAGGCATCTTTGTAT
GCCAGGCAGCAGCTGAACGTCCGGAATGTGGCCAATAACATCTTGGCCA

2 / 4 6

FIG. 1B

TTGCTGCTTTCTTGCCGGCGTGTCGCCCCCACCTGCGACGATATTTCTG
TGCCATTGTCCAGCTGCCTTCTGACTGGATCCAGGTGGCTGAGCTTTAC
CAGAGCCTGGCTGAGGGAGATAAGAATAAGCTGGTGCCCCTGCCCGCCT
GTCTCCGTACTGCCATGACGGACAAATTTGCCCAGTTTGACGAGTACCA
GCTGGCTAAGTACAACCCTCGGAAGCACCGGGCCAAGAGACACCCCCGC
CGGCCACCCCGCTCTCCAGGGATGGAGCCTCCATTTTCTCACAGATGTT
TTCCAAGGTACATAGGGTTTCTCAGAGAAGAGCAGAGAAAGTTTGAGAA
GGCCGGTGATACAGTGTGAGAGAAAAGAATCCTCCAAGGTTACCCCTG
AAGAAGCTGGTTCAGCGACTGCACATCCACAAGCCTGCCCAGCACGTTC
AAGCCCTGCTGGGTACAGATACCCCTCCAACCTACAGCTCTTTTCTCG
AAGTCGCCTTCCTGGGCCTTGGGATTCTAGCAGAGCTGGGAAGAGGATG
AAGCTGTCTAGGCCAGAGACCTGGGAGCGGGAGCTGAGCCTACGGGGGA
ACAAAGCGTCGGTCTGGGAGGAACCTCATTGAAAATGGGAAGCTTCCCTT
CATGGCCATGCTTCGGAACCTGTGCAACCTGCTGCGGGTTGGAATCAGT
TCCCGCCACCATGAGCTCATTCTCCAGAGACTCCAGCATGGGAAGTCGG
TGATCCACAGTCGGCAGTTTCCATTCAGATTTCTTAACGCCCATGATGC
CATTGATGCCCTCGAGGCTCAACTCAGAAATCAAGCATTGCCCTTTCTCT
TCGAATATAACACTGATGAGGCGGATACTAACTAGAAATGAAAAGAACC
GTCCCAGGCGGAGGTTTCTTTGCCACCTAAGCCGTCAGCAGCTTCGTAT

3 / 4 6

FIG. 1C

GGCAATGAGGATACCTGTGTTGTATGAGCAGCTCAAGAGGGAGAAGCTG
AGAGTACACAAGGCCAGACAGTGGAATATGATGGTGAGATGCTGAACA
GGTACCGACAGGCCCTAGAGACAGCTGTGAACCTCTCTGTGAAGCACAG
CCTGCCCCCTGCTGCCAGGCCGCACTGTCTTGGTCTATCTGACAGATGCT
AATGCAGACAGGCTCTGTCCAAAGAGCAACCCACAAGGGCCCCCGCTGA
ACTATGCACTGCTGTTGATTGGGATGATGATCACGAGGGCGGAGCAGGT
GGACGTCGTGCTGTGTGGAGGTGACACTCTGAAGACTGCAGTGCTTAAG
GCAGAAGAAGGCATCCTGAAGACTGCCATCAAGCTCCAGGCTCAAGTCC
AGGAGTTTGATGAAAATGATGGATGGTCCCTGAATACTTTTGGGAAATA
CCTGCTGTCTCTGGCTGGCCAAAGGGTTCTGTGGACAGGGTCATCCTC
CTTGGCCAAAGCATGGATGATGGAATGATAAATGTGGCCAAACAGCTTT
ACTGGCAGCGTGTGAATTCCAAGTGCCTCTTTGTTGGTATCCTCCTAAG
AAGGGTACAATACCTGTCAACAGATTTGAATCCCAATGATGTGACACTC
TCAGGCTGTACTGATGCGATACTGAAGTTCATTGCAGAGCATGGGGCCT
CCCATCTTCTGGAACATGTGGGCCAAATGGACAAAATATTCAAGATTCC
ACCACCCCCAGGAAAGACAGGGGTCCAGTCTCTCCGGCCACTGGAAGAG
GACACTCCAAGCCCCTTGGCTCCTGTTTCCCAGCAAGGATGGCGCAGCA
TCCGGCTTTTCATTTTCATCCACTTTCCGAGACATGCACGGGGAGCGGGA
CCTGCTGCTGAGGTCTGTGCTGCCAGCACTGCAGGCCCGAGCGGCCCT

4 / 46

FIG. 1D

CACCGTATCAGCCTTCACGGAATCGACCTCCGCTGGGGCGTCACTGAGG
AGGAGACCCGTAGGAACAGACAACCTGGAAGTGTGCCTTGGGGAGGTGGA
GAACGCACAGCTGTTTGTGGGGATTCTGGGCTCCCGTTATGGATACATT
CCCCCAGCTACAACCTTCCTGACCATCCACACTTCCACTGGGCCCAGC
AGTACCCTTCAGGGCGCTCTGTGACAGAGATGGAGGTGATGCAGTTCCT
GAACCGGAACCAACGTCTGCAGCCCTCTGCCCAAGCTCTCATCTACTTC
CGGGATTCCAGCTTCCTCAGCTCTGTGCCAGATGCCTGGAAATCTGACT
TTGTTTCTGAGTCTGAAGAGGCCGCATGTCGGATCTCAGAACTGAAGAG
CTACCTAAGCAGACAGAAAGGGATAACCTGCCGCAGATACCCCTGTGAG
TGGGGGGGTGTGGCAGCTGGCCGGCCCTATGTTGGCGGGCTGGAGGAGT
TTGGGCAGTTGGTTCTGCAGGATGTATGGAATATGATCCAGAAGCTCTA
CCTGCAGCCTGGGGCCCTGCTGGAGCAGCCAGTGTCCATCCCAGACGAT
GACTTGGTCCAGGCCACCTTCAGCAGCTGCAGAAGCCACCGAGTCCTG
CCCGGCCACGCCTTCTTCAGGACACAGTGCAACAGCTGATGCTGCCCCA
CGGAAGGCTGAGCCTGGTGACGGGGCAGTCAGGACAGGGCAAGACAGCC
TTCCTGGCATCTCTTGTGTCAGCCCTGCAGGCTCCTGATGGGGCCAAGG
TGGCACCATTAGTCTTCTTCCACTTTTCTGGGGCTCGTCCTGACCAGGG
TCTTGCCCTCACTCTGCTCAGACGCCTCTGTACCTATCTGCGTGGCCAA
CTAAAAGAGCCAGGTGCCCTCCCCAGCACCTACCGAAGCCTGGTGTGGG

5 / 4 6

FIG.1E

AGCTGCAGCAGAGGCTGCTGCCCAAGTCTGCTGAGTCCCTGCATCCTGG
CCAGACCCAGGTCCTGATCATCGATGGGGCTGATAGGTTAGTGGACCAG
AATGGGCAGCTGATTTTCAGACTGGATCCCAAAGAAGCTTCCCCGGTGTG
TACACCTGGTGCTGAGTGTGTCTAGTGATGCAGGCCTAGGGGAGACCCT
TGAGCAGAGCCAGGGTGCCACGTGCTGGCCTTGGGGCCTCTGGAGGCC
TCTGCTCGGGCCCGGCTGGTGAGAGAGGAGCTGGCCCTGTACGGGAAGC
GGCTGGAGGAGTCACCATTTAACAACCAGATGCGACTGCTGCTGGTGAA
GCGGGAATCAGGCCGGCCGCTCTACCTGCGCTTGGTCACCGATCACCTG
AGGCTCTTCACGCTGTATGAGCAGGTGTCTGAGAGACTCCGGACCCTGC
CTGCCACTGTCCCCCTGCTGCTGCAGCACATCCTGAGCACACTGGAGAA
GGAGCACGGGCCTGATGTCCTTCCCCAGGCCTTGACTGCCCTAGAAGTC
ACACGGAGTGGTTTGACTGTGGACCAGCTGCACGGAGTGCTGAGTGTGT
GGCGGACACTACCGAAGGGGACTAAGAGCTGGGAAGAAGCAGTGGCTGC
TGGTAACAGTGGAGACCCCTACCCCATGGGCCCGTTTGCCTGCCTCGTC
CAGAGTCTGCGCAGTTTGCTAGGGGAGGGCCCTCTGGAGCGCCCTGGTG
CCCGGCTGTGCCTCCCTGATGGGCCCCCTGAGAACAGCAGCTAAACGTTG
CTATGGGAAGAGGCCAGGGCTAGAGGACACGGCACACATCCTCATTGCA
GCTCAGCTCTGGAAGACATGTGACGCTGATGCCTCAGGCACCTTCCGAA
GTTGCCCTCCTGAGGCTCTGGGAGACCTGCCTTACCACCTGCTCCAGAG

6 / 46

FIG. 1F

CGGGAACCGTGGACTTCTTTTCGAAGTTCCTTACCAACCTCCATGTGGTG
GCTGCACACTTGGAATTGGGTCTGGTCTCTCGGCTCTTGGAGGCCCATG
CCCTCTATGCTTCTTCAGTCCCCAAAGAGGAACAAAAGCTCCCCGAGGC
TGACGTTGCAGTGTTTCGCACCTTCCTGAGGCAGCAGGCTTCAATCCTC
AGCCAGTACCCCCGGCTCCTGCCCCAGCAGGCAGCCAACCAGCCCCTGG
ACTCACCTCTTTGCCACCAAGCCTCGCTGCTCTCCCGGAGATGGCACCT
CCAACACACACTACGATGGCTTAATAAACCCCGGACCATGAAAAATCAG
CAAAGCTCCAGCCTGTCTCTGGCAGTTTCCTCATCCCCTACTGCTGTGG
CCTTCTCCACCAATGGGCAAAGAGCAGCTGTGGGCACTGCCAATGGGAC
AGTTTACCTGTTGGACCTGAGAACTTGGCAGGAGGAGAAGTCTGTGGTG
AGTGGCTGTGATGGAATCTCTGCTTGTTTGTTCCTCTCCGATGATACAC
TCTTTCTTACTGCCTTCGACGGGCTCCTGGAGCTCTGGGACCTGCAGCA
TGGTTGTCGGGTGCTGCAGACTAAGGCTCACCAGTACCAAATCACTGGC
TGCTGCCTGAGCCCAGACTGCCGGCTGCTAGCCACCGTGTGCTTGGGAG
GATGCCTAAAGCTGTGGGACACAGTCCGTGGGCAGCTGGCCTTCCAGCA
CACCTACCCCAAGTCCCTGAACTGTGTTGCCTTCCACCCAGAGGGGCAG
GTAATAGCCACAGGCAGCTGGGCTGGCAGCATCAGCTTCTTCCAGGTGG
ATGGGCTCAAAGTCACCAAGGACCTGGGGGCACCCGGAGCCTCTATCCG
TACCTTGGCCTTCAATGTGCCTGGGGGGGTTGTGGCTGTGGGCCGGCTG

7 / 46

FIG. 1G

GACAGTATGGTGGAGCTGTGGGCCTGGCGAGAAGGGGCACGGCTGGCTG
CCTTCCCTGCCCACCATGGCTTTGTTGCTGCTGCGCTTTTCCTGCATGC
GGGTTGCCAGTTACTGACGGCTGGAGAGGATGGCAAGGTTTCAGGTGTGG
TCAGGGTCTCTGGGTGCGCCCCGTGGGCACCTGGGTTCCTTTCTCTCT
CTCCTGCCCTCTCTGTGGCACTCAGCCCAGATGGTGATCGGGTGGCTGT
TGGATATCGAGCGGATGGCATTAGGATCTACAAAATCTCTTCAGGTTCC
CAGGGGGCTCAGGGTCAGGCACTGGATGTGGCAGTGTCCGCCCTGGCCT
GGCTAAGCCCCAAGGTATTGGTGAGTGGTGCAGAAGATGGGTCCTTGCA
GGGCTGGGCACTCAAGGAATGCTCCCTTCAGTCCCTCTGGCTCCTGTCC
AGATTCCAGAAGCCTGTGCTAGGACTGGCCACTTCCCAGGAGCTCTTGG
CTTCTGCCTCAGAGGATTTACAGTGCAGCTGTGGCCAAGGCAGCTGCT
GACGCGGCCACACAAGGCAGAAGACTTTCCTGTGGCACTGAGCTGCGG
GGACATGAGGGCCCTGTGAGCTGCTGTAGTTTCAGCACTGATGGAGGCA
GCCTGGCCACCGGGGGCCGGGATCGGAGTCTCCTCTGCTGGGACGTGAG
GACACCCAAAACCCCTGTTTTGATCCACTCCTTCCCTGCCTGTCACCGT
GACTGGGTCACTGGCTGTGCCTGGACCAAAGATAACCTACTGATATCCT
GCTCCAGTGATGGCTCTGTGGGGCTCTGGGACCCAGAGTCAGGACAGCG
GCTTGGTCAGTTCCTGGGTGATCAGAGTGCTGTGAGCGCTGTGGCAGCT
GTGGAGGAGCACGTGGTGTCTGTGAGCCGGGATGGGACCTTGAAAGTGT

8 / 4 6

FIG. 1H

GGGACCATCAAGGCGTGGAGCTGACCAGCATCCCTGCTCACTCAGGACC
CATTAGCCACTGTGCAGCTGCCATGGAGCCCCGTGCAGCTGGACAGCCT
GGGTCAGAGCTTCTGGTGGTAACCGTCGGGCTAGATGGGGCCACACGGT
TATGGCATCCACTCTTGGTGTGCCAAACCCACACCCTCCTGGGACACAG
CGGCCCAGTCCGTGCTGCTGCTGTTTCAGAAACCTCAGGCCTCATGCTG
ACCGCCTCTGAGGATGGTTCTGTACGGCTCTGGCAGGTTCTAAGGAAG
CAGATGACACATGTATACCAAGGAGTTCTGCAGCCGTCACTGCTGTGGC
TTGGGCACCAGATGGTTCCATGGCAGTATCTGGAAATCAAGCTGGGGAA
CTAATCTTGTGGCAGGAAGCTAAGGCTGTGGCCACAGCACAGGCTCCAG
GCCACATTGGTGCTCTGATCTGGTCCTCGGCACACACCTTTTTTGTCTT
CAGTGCTGATGAGAAAATCAGCGAGTGGCAAGTGAACTGCGGAAGGGT
TCGGCACCCGGAAATTTGAGTCTTCACCTGAACCGAATTCTACAGGAGG
ACTTAGGGGTGCTGACAAGTCTGGATTGGGCTCCTGATGGTCACTTTCT
CATCTTGGCCAAAGCAGATTTGAAGTTACTTTGCATGAAGCCAGGGGAT
GCTCCATCTGAAATCTGGAGCAGCTATACAGAAAATCCTATGATATTGT
CCACCCACAAGGAGTATGGCATATTTGTCTTGCAGCCCAAGGATCCTGG
AGTTCTTTCTTTCTTGGAGGCAAAGGAATCAGGAGAGTTTGAAGAGAGG
CTGAACTTTGATATAAACTTAGAGAATCCTAGTAGGACCCTAATATCGA
TAACTCAAGCCAAACCTGAATCTGAGTCCTCATTTTTTGTGTGCCAGCTC

9 / 46

FIG. 11

TGATGGGATCCTATGGAACCTGGCCAAATGCAGCCCAGAAGGAGAATGG
ACCACAGGTAACATGTGGCAGAAAAAGCAAACACTCCAGAAACCCAAA
CTCCAGGGACAGACCCATCTACCTGCAGGGAATCTGATGCCAGCATGGA
TAGTGATGCCAGCATGGATAGTGAGCCAACACCACATCTAAAGACACGG
CAGCGTAGAAAGATTCACTCGGGCTCTGTCACAGCCCTCCATGTGCTAC
CTGAGTTGCTGGTGACAGCTTCGAAGGACAGAGATGTTAAGCTATGGGA
GAGACCCAGTATGCAGCTGCTGGGCCTGTTCCGATGCGAAGGGTCAGTG
AGCTGCCTGGAACCTTGGCTGGGCGCTAACTCCACCCTGCAGCTTGCCG
TGGGAGACGTGCAGGGCAATGTGTACTTTCTGAATTGGGAA

10 / 46

FIG.2A

ATGGAGAAGCTCTGTGGGCATGTGCCTGGCCATTCAGACATCCTCTCCT
TGAAGAACCGGTGCCTGACCATGCTCCCTGACCTCCAGCCCCTGGAGAA
AATACATGGACATAGATCTGTCCACTCAGACATCCTTTCTTGGAGAAC
CAGTGTCTGACCATGCTCTCTGACCTCCAGCCCACGGAGAGAATAGATG
GGCATATATCTGTCCACCCAGACATCCTCTCCTTGGAGAATCGGTGCCT
GACCATGCTCCCTGACCTCCAGCCTCTGGAGAAGCTATGTGGACATATG
TCTAGTCATCCAGACGTCCTTTCTTTGGAAAACCAATGTCTAGCTACTC
TCCCCACTGTAAAGAGCACTGCATTGACCAGCCCCCTTGCTCCAGGGTCT
TCACATATCTCATAACGGCACAAGCTGATCTGCATAGCCTGAAAAC TAGC
AACTGCCTGCTCCCTGAGCTTCCTACCAAGAAGACTCCATGTTTCTCTG
AGGAACTAGACCTTCCACCTGGACCCAGGGCCCTGAAATCCATGTCTGC
TACAGCTCAAGTCCAGGAAGTAGCCTTGGGTCAATGGTGTGTCTCCAAA
GAAAAGGAATTTCAAGAAGAAGAAAGCACAGAAGTCCCRATGCCTTTGT
ACAGTCTAAGCTTGGAAGAAGAAGAAGTGGAGGCACCGGTCTTAAACT
CACATCTGGAGACTCTGGCTTTTCATCCTGAAACCACTGACCAGGTCCCT
CAGGAGAAGAAGATGGCTCTCTTGACCTTACTCTGCTCTGCTCTGGCCT
CAAATGTGAATGTGAAAGATGCATCTGACCTTACCCGGGCATCCATCCT
TGAAGTCTGTAGTGCCCTGGCCTCCTTGGAACCGGAGTTCATCCTTAAG
GCATCTTTGTATGCTCGGCAGCAACTTAACCTCCGGGACATCGCCAATA

11 / 46

FIG.2B

CAGTTCTGGCTGTGGCTGCCCTCTTGCCAGCCTGCCGCCCCCATGTACG
ACGGTATTACTCCGCCATTGTTTACCTGCCTTCAGACTGGATCCAGGTA
GCCGAGTTCTACCAGAGCCTGGCAGAAGGGGATGAGAAGAAGTTGGTGT
CCCTGCCTGCCTGTCTCCGAGCTGCCATGACCGACAAATTTGCCGAGTT
TGATGAGTACCAGCTAGCTAAGTACAACCCACGGAAACATCGGTCCAAG
AGGCGGTCCCGCCAGCCACCCCGCCCTCAAAGACAGAACGTCCATTTT
CAGAGAGAGGGAAATGTTTTCCAAAGAGCCTTTGGCCCCCTTAAAAATGA
ACAGATTACGTTTGAAGCAGCTTATAATGCAATGCCAGAGAAAAACAGG
CTACCACGGTTCCTCTGAAGAAGTTGGTAGAGTATCTACATATCCACA
AGCCTGCTCAGCACGTCCAGGCCCTGCTGGGCTACAGGTACCCAGCCAC
CCTAGAGCTCTTTTCTCGGAGTCACCTCCCTGGGCCGTGGGAGTCTAGC
AGAGCTGGTCAGCGGATGAAGCTCCGAAGGCCAGAGACCTGGGAGCGGG
AGCTGAGTTTACGGGGAAACAAAGCTTCTGTGTGGGAGGAGCTCATAGA
CAATGGGAAACTGCCCTTCATGGCCATGCTCCGGAACCTGTGTAACCTG
CTGCGGACTGGGATCAGTGCCCGCCACCATGAACTCGTTCTCCAGAGAC
TCCAGCATGAGAAATCTGTGGTTTACAGTCGGCAGTTTCCATTCAGATT
CCTTAATGCTCATGACTCTATCGATAAACTTGAGGCTCAGCTCAGAAGC
AAAGCATCACCTTCCCTTCCAATACAACATTGATGAAACGGATAATGA
TTAGAAACTCAAAAAAAAAATAGGAGGCCTGCCAGTCGGAAGCACCTGTG

1 2 / 4 6

FIG.2C

CACCCTGACGCGCCGGCAGCTTCGGGCAGCAATGACTATACCTGTGATG
TATGAGCAGCTCAAGCGGGAGAACTGAGGCTGCACAAGGCCAGACAAT
GGAACGTGATGTTGAGTTGCTGGAGCGCTATCGCCAGGCCCTGGAAAC
AGCTGTGAACCTCTCAGTAAAGCACAACTATCCCCGATGCCTGGCCGA
ACCCTCTTGGTCTATCTCACAGATGCAAATGCCGACAGGCTCTGTCCCA
AGAGTCACTCACAAGGGCCTCCCCTGAACTATGTGCTGCTGCTGATCGG
AATGATGGTGGCTCGAGCCGAGCAAGTGACTGTTTGCTTGTGTGGGGGA
GGATTTGTGAAGACACCGGTACTTACAGCCGATGAAGGCATCCTGAAGA
CTGCCATCAAAC^TTCAGGCTCAAGTCCAGGAGTTAGAAGGCAATGATGA
GTGGCCCCCTGGACACTTTTGGGAAGTATCTGCTGTCTCTGGCTGTCCAA
AGGACCCCCATTGACAGGGTCATCCTGTTTGGTCAAAGGATGGATACCG
AGCTCCTGAAAGTAGCCAAACAGATTATCTGGCAGCATGTGAATTCCAA
GTGCCTCTTTGTTGGTGTCTCCTACAGAAAACACAGTACATATCACCA
AATTTGAATCCCAACGATGTGACGCTCTCAGGCTGCACTGACGGGATCC
TGAAATTCATTGCCGAACATGGAGCCTCTCGTCTCCTGGAACATGTGGG
ACAAC TAGATAAACTATTCAAGATCCCCCACC^CCCAGGAAAGACACAG
GCACCGTCTCTCCGGCCGCTGGAGGAGAACATCCCTGGTCCCTTGGGTC
CTATTTCCCAGCATGGATGGCGCAATATCCGGCTTTTTCATTTCATCCAC
TTTCCGTGACATGCATGGGGAGCGAGATTTGCTGATGAGATCTGTTCTG

13 / 46

FIG.2D

CCCGCACTGCAGGCCAGAGTGTTCCCCCACCGCATCAGTCTTCACGCCA
TTGACCTGCGCTGGGGTATCACAGAGGAAGAGACCCGCAGGAACAGACA
ACTGGAAGTGTGCCTTGGGGAGGTGGAGAACTCACAGCTGTTTCGTGGGG
ATTCTGGGCTCCCGCTATGGCTACATTCCCCCAGCTATGATCTTCCTG
ATCATCCCCACTTTCAGTGGACCCATGAGTACCCTTCAGGGCGATCCGT
GACAGAGATGGAGGTGATGCAATTCCTGAACCGTGGCCAACGCTCGCAG
CCTTCGGCCCAAGCTCTCATCTACTTCCGAGATCCTGATTTCCTTAGCT
CTGTGCCAGATGCCTGGAAACCTGACTTTATATCTGAGTCAGAAGAAGC
TGCACATCGGGTCTCAGAGCTGAAGAGATATCTACACGAACAGAAAGAG
GTTACCTGTTCGCAGCTACTCCTGTGAATGGGGAGGTGTAGCGGCTGGCC
GGCCCTATACTGGGGGCCTGGAGGAGTTTGGACAGTTGGTTCTCCAGGA
TGTGTGGAGCATGATCCAGAAGCAGCACCTGCAGCCTGGGGCCCAGTTG
GAGCAGCCAACATCCATCTCAGAAGACGATTTGATCCAGACCAGCTTTC
AGCAGCTGAAGACCCCAACGAGTCCGGCACGGCCACGCCTTCTTCAGGA
TACAGTGCAGCAGCTGTTGCTGCCCCATGGGAGGCTGAGCCTAGTGACT
GGGCAGGCAGGACAGGGAAAGACTGCCTTTCTGGCATCCCTTGTGTCTG
CCCTGAAGGTCCCTGACCAGCCCAATGAGCCCCCGTTTCGTTTTCTTCCA
CTTTGCAGCAGCCCGCCCTGACCAGTGTCTTGCTCTCAACCTCCTCAGA
CGCCTCTGTACCCATCTGCGTCAAAAAGTGGGAGAGCTGAGTGCCCTCC

1 4 / 4 6

FIG.2E

CCAGCACTTACAGAGGCCTGGTGTGGGAACTGCAGCAGAAGTTGCTCCT
CAAATTCGCTCAGTCGCTGCAGCCTGCTCAGACTTTGGTCCTTATCATC
GATGGGGCAGATAAGTTGGTGGATCGTAATGGGCAGCTGATTTCAGACT
GGATCCCCAAGTCTCTTCCGCGGCGAGTACACCTGGTGTGAGTGTGTC
CAGTGACTCAGGCCTGGGTGAGACCCTTCAGCAAAGTCAGGGTGCTTAT
GTGGTGGCCTTGGGCTCTTTGGTCCCATCTTCAAGGGCTCAGCTTGTGA
GAGAAGAGCTAGCACTGTATGGGAAACGACTGGAGGAGTCACCTTTTAA
CAACCAGATGCGGCTGCTGCTGGCAAAGCAGGGTTCAAGCCTGCCATTG
TACCTGCACCTTGTCACCTGACTACCTGAGGCTCTTCACACTGTATGAAC
AGGTGTCTGAGAGACTTCGAACCCTGCCCCGCACTCTCCCACTGCTCTT
GCAGCACATCCTGAGCACCTTGGAGCAAGAACATGGCCATGATGTCCTT
CCTCAGGCTTTGACTGCCCTTGAGGTCACACGAAGTGGTCTGACTGTGG
ACCAGCTACATGCAATCCTGAGCACATGGCTGATCTTGCCCAAGGAGAC
TAAGAGCTGGGAAGAAGTGCTGGCTGCCAGTCACAGTGGAACCCCTTTC
CCCTTGTTGCCATTTGCCTACCTTGTCAGAGTCTACGCAGTTTACTAG
GGGAGGGCCCAGTGAGCGCCCTGGTGCCCGTCTCTGCCTCTCTGATGG
GCCCCTGAGGACAACAATTAAACGTCGCTATGGGAAAAGGCTGGGGCTA
GAGAAGACTGCGCATGTCCTCATTGCAGCTCACCTCTGGAAGACGTGTG
ATCCTGATGCCTCGGGCACCTTCCGAAGTTGCCCTCCTGAGGCTCTGAA

15 / 46

FIG.2F

AGATTTACCTTACCACCTGCTCCAGAGCGGGAACCATGGTCTCCTTGCC
GAGTTTCTTACCAATCTCCATGTGGTTGCTGCATATCTGGAAGTGGGTC
TAGTCCCCGACCTCTTGGAGGCTCATGTGCTCTATGCTTCTTCAAAGCC
TGAAGCCAACCAGAAGCTCCCAGCGGCAGATGTTGCTGTTTTCCATACC
TTCCTGAGACAACAGGCTTCACTCCTTACCCAGTATCCTTTGCTCCTGC
TCCAGCAGGCAGCTAGCCAGCCTGAAGAGTCACCTGTTTGCTGCCAGGC
CCCCCTGCTCACCCAGCGATGGCACGACCAGTTCACACTGAAATGGATT
AATAAACCCCAGACCCTGAAGGGTCAGCAAAGCTTGTCTCTGACAATGT
CCTCATCCCCAACTGCTGTGGCCTTCTCCCCGAATGGGCAAAGAGCAGC
TGTGGGGACCGCCAGTGGGACAATTTACCTGTTGAACTTGAAAACCTGG
CAGGAGGAGAAGGCTGTGGTGAGTGGCTGTGACGGGATTTCTCTTTTG
CATTCCTTTTCGGACACTGCCCTTTTCCTTACTACCTTCGACGGGCACCT
AGAGCTTTGGGACCTGCAACATGGTTGTTGGGTGTTTCAGACCAAGGCC
CACCAGTACCAAATCACTGGCTGCTGCCTGAGCCCAGACCGCCGCCTGC
TGGCCACTGTGTGTTTGGGAGGATACCTAAAGCTGTGGGACACAGTCCG
AGGACAGCTGGCTTTTCAGTACACCCATCCAAAGTCTCTCAACTGCGTT
GCCTTCCACCCAGAGGGGCAGGTGGTAGCCACAGGCAGCTGGGCTGGCA
GCATTACCTTCTTCCAGGCAGATGGACTCAAAGTCACCAAGGAACTAGG
GGCCCCCGGACCCTCTGTCTGTAGTTTGGCATTCAACAAACCTGGGAAG

16 / 46

FIG.2G

ATTGTGGCTGTGGGCCGGATAGATGGGACAGTGGAGCTGTGGGCCTGGC
AAGAGGGTGCCCGGCTGGCGGCCTTCCCTGCACAGTGTGGCTGTGTCTC
TGCTGTTCTTTTCTTGCATGCTGGAGACCGGTTCTGACTGCTGGAGAA
GATGGCAAGGCTCAGTTATGGTCAGGATTTCTTGGCCGGCCCAGGGGTT
GCCTGGGCTCTCTTCCTCTTTCTCCTGCACTCTCGGTGGCTCTCAACCC
AGACGGTGACCAGGTGGCTGTTGGGTACCGAGAAGATGGCATTAAACATC
TACAAGATTTCTTCAGGTTCCTCAGGGGCCTCAGCATCAAGAGCTAAATG
TGGCGGTGTCTGCACTGGTGTGGCTGAGCCCTAGTGTTTTGGTGAGTGG
TGCAGAAGATGGATCCCTGCATGGTTGGATGTTCAAGGGAGACTCCCTT
CATTCCTGTGGCTGTTGTGCGAGATAACAGAAGCCTGTGCTGGGACTGG
CTGCCTCCCGGGAACATCATGGCTGCTGCCTCAGAGGACTTCACTGTGAG
ACTGTGGCCCAGACAGCTGCTGACACAGCCACATGTGCATGCGGTAGAG
TTGCCCTGTTGTGCTGAACTCCGGGGACACGAGGGGCCAGTGTGCTGCT
GTAGCTTCAGCCCTGATGGAGGCATCTTGGCCACAGCTGGCAGGGATCG
GAATCTCCTTTGCTGGGACATGAAGATAGCCCAAGCCCCCTCTCCTGATT
CACACTTCTCGTCCTGTCATCGTGAAGTCACTGGCTGTGCGTGGA
CCAAAGACAACATCCTGGTCTCCTGCTCGAGTGATGGCTCTGTGGGACT
CTGGAACCCAGAGGCAGGGCAGCAACTTGGCCAGTTCTCAGGCCACCAG
AGTGCCGTGAGCGCCGTGGTTGCTGTGGAGGAACACATTGTATCTGTGA

17 / 46

FIG.2H

GCCGAGATGGGACCTTGAAAGTGTGGGACCATCAGGGTGTGGAGCTGAC
CAGCATCCCTGCCCATTCCGGACCCATCAGCCAGTGTGCAGCTGCTCTG
GAGCCCCGCCCAGGGGGACAGCCTGGATCAGAGCTTCTGGTGGTGACTG
TTGGACTAGATGGGGCCACAAAGTTGTGGCATCCCCTGTTGGTGTGCCA
AATACGTACTCTCCAGGGACACAGTGGCCCAGTCACAGCAGCTGCTGCT
TCAGAGGCCTCAGGCCTCCTGCTGACCTCAGATGATAGCTCTGTACAGC
TCTGGCAGATACCAAAGGAAGCAGATGATTCATACAAACCTAGGAGTTC
TGTGGCCATCACTGCTGTGGCATGGGCACCGGATGGTTCTATGGTGGTG
TCCGGAAATGAAGCCGGGGAACTGACACTGTGGCAGCAAGCCAAGGCTG
TGGCTACCGCACAGGCTCCAGGCCGCGTCAGTCACCTGATCTGGTACTC
GGCAAATTCATTCTTCGTTCTCAGTGCTAATGAAAACGTCAGCGAGTGG
CAAGTGGGACTGAGGAAAGGTTCAACGTCCACCAGTTCCAGTCTTTCATC
TGAAGAGAGTTCTGCAGGAGGACTGGGGAGTCTTGACAGGTCTGGGTCT
GGCCCCCTGATGGCCAGTCTCTCATCTTGATGAAAGAGGATGTGGAATTA
CTAGAGATGAAGCCTGGGTCTATTCCATCTTCTATCTGCAGGAGGTATG
GAGTACATTCTTCAATACTGTGCACCAGCAAGGAGTACGGCTTGTTCTA
CCTGCAGCAGGGGGACTCCGGATTACTTTCTATATTGGAGCAAAGGAG
TCAGGGGAGTTTGAAGAGATCCTGGACTTCAATCTGAACTTAAATAATC
CTAATGGGTCCCCAGTATCAATCACTCAGGCCAAACCTGAGTCTGAATC

18 / 46

FIG.21

ATCCCTTTTGTGCGCCACCTCTGATGGGATGCTGTGGAACCTTATCTGAA
TGTACCTCAGAGGGAGAATGGATCGTAGATAACATTTGGCAGAAAAAAG
CAAAAAAACCTAAAACTCAGACTCTGGAGACAGAGTTGTCCCCGCACTC
AGAGTTGGATTTTTCATTGATTGCTGGATTGATCCCACAAATTTAAAG
GCACAGCAGTGTA AAAAGATCCACTTGGGCTCTGTCACAGCCCTCCATG
TGCTTCCGGGATTGCTGGTGACAGCTTCGAAGGACAGAGATGTTAAGCT
GTGGGAGAGACCCAGTATGCAGCTGCTGGGCTTGTTCCGATGTGAAGGG
CCAGTGAGCTGTCTGGAACCTTGGATGGAGCCCAGCTCTCCCCTGCAGC
TTGCTGTGGGAGACACACAAGGAACTTGTAATTTCTATCTTGGGAA

19 / 40

FIG.3A

MEKLHGHVSAHPDILSLENRCLAMLPDLQPLEKLBHVSTHSDILSLKN
QCLATLPDLKTMEKPHGYVSAHPDILSLENQCLATLSDLKTMEKPHGHV
SAHPDILSLENRCLATLPSLKSTVSASPLFQSLQISHMTQADLYRVNNS
NCLLSEPPSWRAQHFSKGLDLSTCPIALKSISATETAQEATLGRWFDSE
EKKGAETQMPSSLSLGEVEEDLAVKLTSGDSESHPEPTDHVLQEKK
MALLSLLCSTLVSEVNMNNTSDPTLAAIFEICRELALLEPEFILKASLY
ARQQLNVRNVANNILAIAAFLPACRPHLRRYFCAIVQLPSDWIQVAELY
QSLAEGDKNKLVPLPACLRRTAMTDKFAQFDEYQLAKYNPRKHKRAKHPR
RPPRSPGMEPPFSHRCFPRYIGFLREEQRKFEEKAGDTVSEKKNPPRFTL
KKLVQRLHIHKPAQHVQALLGYRYPSNLQLFSRSRLPGPWDSSRAGKRM
KLSRPETWERELSLRGNKASVWEELIENGKLPFMAMLRNLCNLLRVGIS
SRHHELILQRLQHGSVIHSRQFPFRFLNAHDAIDALEAQLRNQALPFP
SNITLMRRILTRNEKNRPRRRFLCHLSRQQLRMAMRIPVLYEQLKREKL
RVHKARQWKYDGEMLNRYRQALETAVNLSVKHSLPLLPGRTVLVYLTDA
NADRLCPKSNPQGPPPLNYALLIGMMITRAEQVDVVLGGDTLKTAVLK
AEEGILKTAIKLQAQVQEFDENDGWSLNTFGKYLLSLAGQRPVDRVIL
LGQSMDDGMINVAKQLYWQRVNSKCLFVGILLRRVQYLSTDLPNDVTL
SGCTDAILKFIAEHGASHLLEHVGQMDKIFKIPPPGKTGVQSLRPLEE
DTPSPLAPVSQQGWSRIRLFISSTFRDMHGERDLLLLRSVLPALQARAAP

20 / 46

FIG.3B

HRISLHGIDLRWGVTEEETRRNRQLEVCLGEVENAQLFVGILGSRYGYI
PPSYNLPDHPHFHWAQQYPSGRSVTEMEVMQFLNRNQRLOPSAQUALIYF
RDSSFLSSVPDAWKSDFFVSESEEAAXRISELKSYLSRQKGITCRRYPCE
WGGVAAGRPYVGGLEEFQQLVLQDVWNMIQKLYLQPGALLEQPVSIPDD
DLVQATFQQLQKPPSPARPRLLQDTVQXLMLPHGRLSLVTGQSGQGKTA
FLASLVSALQAPDGAKVAXLVFFHFSGARPDQGLALTLLRRLCTYLRGQ
LKEPGALPSTYRSLVWELQQRLLPKSAESLHPGQTQVLIIDGADRLVDQ
NGQLISDWIPKKLPRCVHLVLSVSSDAGLGETLEQSQGAHVLAALGPLEA
SARARLVREELALYGKRLEESPFNNQMRLLLVKRESGRPLYLRLVTDHL
RLFTLYEQVSERLRTLTPATVPLLLQHILSTLEKEHGPDVLPQALTALEV
TRSGLTVDQLHGVLSVWRTLPGKTKSWEEAVAAGNSGDPYPMGPFACLV
QSLRSLLGEGPLERPGARLCLPDGPLRTAAKRCYGKRPGLEDTAHILIA
AQLWKTCDADASGTFRSCPPEALGDLPHYLLQSGNRGLLSKFLTNLHV
AAHLELGLVSRLLLEAHALYASSVPKEEQKLPEADVAVFRTFLRQQASIL
SQYPRLLPQQAANQPLDSPLCHQASLLSRRWHLQHTLRWLNKPRMTKNQ
QSSSLSLAVSSSPTAVAFSTNGQRAAVGTANGTVYLLDLRTWQEEKSVV
SGCDGISACLFLSDDTLFLTAFDGLLELWDLQHGCRLVLTQKAHQYQITG
CCLSPDCRLLATVCLGGCLKLWDTV RGQLAFQHTYPKSLNCVAFHPEGQ
VIATGSWAGSISFFQVDGLKVTKDLGAPGASIRTLAFNVPGGVVAVGRL

21 / 46

FIG.3C

DSMVELWAWREGARLAAPFAHHGFVAAALFLHAGCQLLTAGEDGKVQVW
SGSLGRPRGHLGSLSLSPALSVALSPDGDRVAVGYRADGIRIYKISSGS
QGAQQQALDVAVSALAWLSPKVLVSGAEDGSLQGWALKECSLQSLWLLS
RFQKPVLGLATSQELLASASEDFTVQLWPRQLLTRPHKAEDFPCGTELR
GHEGPVSCCSFSTDGGSLATGGRDRSLLCWDVRTPKTPVLIHSFPACHR
DWVTGCAWTKDNLLISCSSDGSVGLWDPESGQRLGQFLGHQSAVSAVAA
VEEHVVSVRDGTKVWDHQGVELTSIPAHS GPI SHCAAAMEPRAAGQP
GSELLVVTVGLDGATRLWHPLLCVQTHLLGHSGPVRAAAVSETSGMLML
TASEDGSVRLWQVPKEADDTICIPSSAAVTAVAWAPDGSMASVSGNQAGE
LILWQEAKAVATAQAPGHIGALIWSSAHTFFVLSADEKISEWQVKLRKG
SAPGNLSLHLNRILQEDLGVLTSLDWAPDGHFLILAKADLKLKCMKPGD
APSEIWSSYTENPMILSTHKEYGIFVLQPKDPGVLSFLRQKESGEFEER
LNFDINLENPSRTLISITQAKPESESSFLCASSDGILWNLAKCSPEGEW
TTGNMWQKKANTPETQTPGTD PSTCRES DASMDSDASMDSEPTPHLKTR
QRRKIHSGSVTALHVLPELLVTASKDRDVKLWERPSMQLLGLFRCEGSV
SCLEPWLGANSTLQLAVGDVQGNVYFLNWE

22 / 46

FIG.4A

MEKLCGHVPGHSDILSLKNRCLTMLPDLQPLEKIHGHRVHSDILSLEN
QCLTMLSDDLQPTERIDGHISVHPDILSLENRCLTMLPDLQPLEKLCGHM
SSHPDVLLENQCLATLPTVKSTALTSPLLQGLHISHTAQADLHSLKTS
NCLLPELPTKKTPCFSEELDLPPGPRALKSMSATAQVQEVAGQWCVSK
EKEFQEEESTEVPMPLYSLSEEEEEVEAPVLKLTSGDSGFHPETTDQVL
QEKKMA LLTLLCSALASNVNVKDASDLTRASILEVCSALASLEPEFILK
ASLYARQQLNLRDIANTVLAVAALLPACRPHVRRYSAIVHLPSDWIQV
AEFYQSLAEGDEKKLVSLPACLRAAMTDKFAEFDEYQLAKYNPRKHRSK
RRSRQPPRPQKTERPFSERGKCFPKSLWPLKNEQITFEAAYNAMPEKNR
LPRFTLKKLVEYLHIHKPAQHVAQALLGYRYPATLELFSRSHLPGPWESS
RAGQRMKLRPETWERELSLRGNKASVWEELIDNGKLPFMAMLRNLCNL
LRTGISARHHELVLQRLQHEKSVVHSRQFPFRFLNAHDSIDKLEAQLRS
KASPFPSNTTLMKRIMIRNSKKNRRPASRKHLCTLTRQLRAAMTIPVM
YEQLKREKLRLHKARQWNCVVELLERYRQALETAVNLSVKHNLSMPMGR
TLLVYLTDANADRLCPKSHSQGPPLNYVLLLLIGMMVARAEQVTVCLCGG
GFVKTPVLTADGILKTAIKLQAQVQELEGNDEWPLDTFGKYLLSLAVQ
RTPIDRVILFGQRMDELLKQVAKQIIWQHVNSKCLFVGVLQKTQYISP
NLNPNDVTLTGCTDGILKFIAEHGASRLLEHVGQLDKLFKIPPPPGKTQ
APSLRPLEENIPGPLGPISQHGWRNIRLFISSTFRDMHGERDLLMRSVL

23 / 46

FIG.4B

PALQARVFPHRISLHAIDLRWGITTEEETRRNRQLEVCLGEVENSQLEFVG
ILGSRYGYIPPSYDLPDHPHFHWTHEYPSGRSVTEMEVMQFLNRGQRSQ
PSAQUALIYFRDPDFLSSVPDAWKPDFISESEEAHRVSELKRYLHEQKE
VTCRSYSCEWGGVAAGRPYTGGLEEFQQLVLQDVWSMIQKQHLQPGAQL
EQPTSISEDCLIQTSFQQLKTPTSPARPRLLQDTVQQLLLPHGRLSLVT
GQAGQGKTAFLASLVSALKVDPQNEPPFVFFHFAAARPDQCLALNLLR
RLCTHLRQKLGELSALPSTYRGLVWELQQKLLKFAQSLQPAQTLVLII
DGADKLVDNRNGQLISDWIPKSLPRRVHLVLSVSSDSGLGETLQQSQGAY
VVALGSLVPSSRAQLVREELALYGKRLEESPFNNQMRLLLAKQGSSPL
YLHLVTDYLRFLTLYEQVSERLRTLPLLLQHILSTLEQEHGHDVL
PQALTALEVTRSGLTVDQLHAILSTWLILPKETKSWEVLAASHSGNPF
PLCPFAYLVQSLRSLLGEGPVERPGARLCLSDGPLRTTIKRRYGKRLGL
EKTAHVLIAAHLWKTCDPDASGTFRSCPPEALKDLPYHLLQSGNHGLLA
EFLTNLHVVAAYLEVGLVPDLLEAHVLYASSKPEANQKLPAADVAVFHT
FLRQQASLLTQYPLLLLQQAASQPEESPVCCQAPLLTQRWHDQFTLKWI
NKPQTLKGQQSLSLTMSSSPTAVAFSPNGQRAAVGTASGTIYLLNLKTW
QEEKAVVSGCDGISSFAFLSDTALFLTTFDGHLELWDLQHGCWVFQTKA
HQYQITGCCLSPDRRLLATVCLGGYKLWDTVRGQLAFQYTHPKSLNCV
AFHPEGQVVATGSWAGSITFFQADGLKVTKELGAPGPSVCSLAFNKP GK

24 / 46

FIG.4C

IVAVGRIDGTVELWAWQEGARLAAFPAQCGCVSAVLFLHAGDRFLTAGE
DGKAQLWSGFLGRPRGCLGSLPLSPALSVALNPDGDQVAVGYREDGINI
YKISSGSQGPQHQELNVAVSALVWLSPSVLVSGAEDGSLHGWMFKGDSL
HSLWLLSRYQKPVGLAASRELMAAASEDFTVRLWPRQLLTQPHVHAVE
LPCCAELRGHEGPVCCCSFSPDGGILATAGRDRNLLCWDMMKIAQAPLLI
HTFSSCHRDWITGCAWTKDNILVSCSSDGSVGLWNPEAGQQLGQFSGHQ
SAVSAVVAVEEHIVSVSRDGTCLKVWDHQVELTSIPAHS GPISQCAAAL
EPRPGGQPGSELLVVTVGLDGATKLWHPLLVCQIRTLOGHSGPVTAAAA
SEASGLLLTSDDSSVQLWQIPKEADDSYKPRSSVAITAVAWAPDGS MVV
SGNEAGELTLWQQAKAVATAQAPGRVSHLIWYSANSFFVLSANENVSEW
QVGLRKGSTSTSSSLHLKRVLQEDWGVLTGLGLAPDGQSLILMKEDVEL
LEMKPGSIPSSICRRYGVHSSILCTSKEYGLFYLOQGD SGLLSILEQKE
SGEFEEILDFNLNLNPNNGSPVSITQAKPESESSLLCATSDGMLWNLSE
CTSEGEWIVDNIWQKKAKKPKTQTLETELSPHSELDFSIDCWIDPTNLK
AQQCKKIHLSVTALHVLPGLLVTASKDRDVKLWERPSMQLLGLFRCEG
PVSCLEPWMEPSSPLQLAVGDTQGNLYFLSWE

25 / 46

FIG.5A

CACGCGTCCGGGCAGCGCTGCGTCCTGCTGCGCACGTGGGAAGCCCTGG
CCCCGGCCACCCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCGTGCG
CTCCCTGCTGCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTC
GTGCGGCGCCTGGGGCCCCAGGGCTGGCGGCTGGTGCAGCGCGGGGACC
CGGCGGCTTTCCGCGCGCTGGTGGCCCAGTGCCCTGGTGTGCGTGCCCTG
GGACGCACGGCCGCCCCCGCCGCCCCCTCCTTCCGCCAGGTGTCCTGC
CTGAAGGAGCTGGTGGCCCGAGTGCTGCAGAGGCTGTGCGAGCGCGGCG
CGAAGAACGTGCTGGCCTTCGGCTTCGCGCTGCTGGACGGGGCCCCGCGG
GGGGCCCCCGAGGCCTTCACCACCAGCGTGCGCAGCTACCTGCCCAAC
ACGGTGACCGACGCACTGCGGGGGAGCGGGGCGTGGGGGCTGCTGCTGC
GCCGCGTGGGCGACGACGTGCTGGTTACCTGCTGGCACGCTGCGCGCT
CTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCCG
CTGTACCAGCTCGGCGCTGCCACTCAGGCCCGGCCCCCGCCACACGCTA
GTGGACCCCGAAGGCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGT
CAGGGAGGCCGGGGTCCCCCTGGGCCTGCCAGCCCCGGGTGCGAGGAGG
CGCGGGGGCAGTGCCAGCCGAAGTCTGCCGTTGCCCAAGAGGCCAGGC
GTGGCGCTGCCCCCTGAGCCGGAGCGGACGCCCCGTTGGGCAGGGGTCTTG
GGCCCACCCGGGCAGGACGCGTGACCGAGTGACCGTGGTTTCTGTGTG
GTGTCACCTGCCAGACCCGCCGAAGAAGCCACCTCTTTGGAGGGTGCGC

26 / 46

FIG.5B

TCTCTGGCACGCGCCACTCCCACCCATCCGTGGGCGCCAGCACCACGC
GGGCCCCCATCCACATCGCGGCCACCACGTCCCTGGGACACGCCTTGT
CCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTCAGGCGACA
AGGAGCAGCTGCGGCCCTCCTTCCTACTCAGCTCTCTGAGGCCAGCCT
GACTGGCGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCCAGGCCC
TGGATGCCAGGACTCCCCGCAGGTTGCCCCGCCTGCCCCAGCGCTACT
GGCAAATGCGGCCCTGTTCCTGAGCTGCTTGGGAACCACGCGCAGTG
CCCCTACGGGGTGCTCCTCAAGACGCACTGCCCGCTGCGAGCTGCGGTC
ACCCAGCAGCCGGTGTCTGTGCCCCGGGAGAAGCCCCAGGGCTCTGTGG
CGGCCCCGAGGAGGAGGACACAGACCCCCGTCGCCTGGTGCAGCTGCT
CCGCCAGCACAGCAGCCCCTGGCAGGTGTACGGCTTCGTGCGGGCCTGC
CTGCGCCGGCTGGTGCCCCCAGGCCTCTGGGGCTCCAGGCACAACGAAC
GCCGCTTCCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCATGC
CAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCGGGACTGC
GCTTGCTGCGCAGGAGCCCAGGGGTGGCTGTGTTCCGGCCGCAGAGC
ACCGTCTGCGTGAGGAGATCCTGGCCAAGTTCCTGCACTGGCTGATGAG
TGTGTACGTCGTCGAGCTGCTCAGGTCTTTCTTTTATGTCACGGAGACC
ACGTTTCAAAGAAGCAGGCTCTTTTCTACCGGAAGAGTGTCTGGAGCA
AGTTGCAAAGCATTGGAATCAGACAGCACTTGAAGAGGGTGCAGCTGCG

27 / 46

FIG.5C

GGAGCTGTCGGAAGCAGAGGTCAGGCAGCATCGGGAAGCCAGGCCCGCC
CTGCTGACGTCCAGACTCCGCTTCATCCCCAAGCCTGACGGGCTGCGGC
CGATTGTGAACATGGACTACGTCGTGGGAGCCAGAACGTTCCGCAGAGA
AAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACTGTTACGCGTG
CTCAACTACGAGCGGGCGCGGGCGCCCCGGCCTCCTGGGCGCCTCTGTGC
TGGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGT
GCGGGCCCAGGACCCGCGCCTGAGCTGTACTTTGTCAAGGTGGATGTG
ACGGGCGCGTACGACACCATCCCCAGGACAGGCTCACGGAGGTCATCG
CCAGCATCATCAAACCCCAGAACACGTACTGCGTGCGTCGGTATGCCGT
GGTCCAGAAGGCCGCCCATGGGCACGTCCGCAAGGCCTTCAAGAGCCAC
GTCTCTACCTTGACAGACCTCCAGCCGTACATGCGACAGTTTCGTGGCTC
ACCTGCAGGAGACCAGCCCGCTGAGGGATGCCGTCGTCATCGAGCAGAG
CTCCTCCCTGAATGAGGCCAGCAGTGGCCTCTTCGACGTCTTCCTACGC
TTCATGTGCCACCACGCCGTGCGCATCAGGGGCAAGTCCTACGTCCAGT
GCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCTGCAGCCT
GTGCTACGGCGACATGGAGAACAAGCTGTTTGCGGGGATTCGGCGGGAC
GGGCTGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACC
TCACCCACGCGAAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGA
GTATGGCTGCGTGGTGAACCTTGCGGAAGACAGTGGTGAACCTTCCTGTA

WO 98/21343

PCT/US97/21248 -

28 / 46

FIG.5D

GAAGACGAGGCCCTGGGTGGCACGGCTTTTGTTTCAGATGCCGGCCCCACG

GCCTAT

29 / 46

FIG. 6A

HASGQRCVLLRTWEALAPATPAMPRAPRCRAVRSLLRSHYREVLPLATF
VRRLGPQGWRLVQRGDPAAFRALVAQCLVCVPWDARPPPAAPSFRQVSC
LKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPN
TVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPP
LYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARR
RGGASASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCV
VSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPC
PPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRP
WMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLRAAV
TPAAGVCAREKPQGSVAAPEEEDTDPRRLVQLLRQHSSPWQVYGFVRAC
LRRLVPPGLWGSRHNERFLRNTKKFISLGKHAKLSLQELTWKMSVRDC
AWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTET
TFQKNRLFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPA
LLTSRLRFIPKPDGLRPVNM DYVVGARTFRREKRAERLTSRVKALFSV
LNYERARRPGLLGASVLGLDDIHRAWRTFVL RVRAQDPPPELYFVKVDV
TGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSH
VSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLR
FMCHHAVRIRGKSYVQCQGIPOGSILSTLLCSLCYGD MENKLFAGIRRD

WO 98/21343

PCT/US97/21248 -

30 / 46

FIG.6B

GLLLRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFV

EDEALGGTAFVQMPAHL

WO 98/21343

PCT/US97/21248

3 1 / 4 6

FIG. 7

TCCCCTGGTGCGGCCTGCTGCTGGATACCCGGACCCTGGAGGTGCAGAGCGACT
ACTCCAGCTATGCCCCGGACCTCCATCAGAGCCAGTCTCACCTTCAACCGCGGCT
TCAAGGCTGGGAGGAACATGCGTCGCAAACCTCTTTGGGGTCTTGCGGCTGAAGT
GTCACAGCCTGTTTCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCA
ACATCTACAAGATCCTCCTGCTGCAGGCGTACAGGTTTCACGCATGTGTGCTGC
AGCTCCCATTTTCATCAGCAAGTTTGGAAGAACCCACATTTTTCTGCGCGTCA
TCTCTGACACGGCCTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGA
TGTCGCTGGGGGCCAAGGGCGCCGCCGCCCTCTGCCCTCCGAGGCCGTGCAGT
GGCTGTGCCACCAAGCATTCCTGCTCAAGCTGACTCGACACCGTGTACCTACG
TGCCACTCCTGGGGTCACTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCC
CGGGGACGACGCTGACTGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAG
ACTTCAAGACCATCCTGGACTGATGGCCACCCGCCACAGCCAGGCCGAGAGCA
GACACCAGCAGCCCTGTCACGCCGGGCTCTACGTCCCAGGGAGGGAGGGGCGGC
CCACACCCAGGCCCGCACCGCTGGGAGTCTGAGGCCTGAGTGAGTGTTTGCCG
AGGCCTGCATGTCCGGCTGAAGGCTGAGTGTCCGGCTGAGGCCTGAGCGAGTGT
CCAGCCAAGGGCTGAGTGTCCAGCACACCTGCCGTCTTCACTTCCCCACAGGCT
GGCGCTCGGCTCCACCCAGGGCCAGCTTTTCTCTACCAGGAGCCCGGCTTCCA
CTCCCCACATAGGAATAGTCCATCCCCTGAT

3 2 / 4 6
FIG.8A

CCACGCGTCCGGGCAGCGCTGCGTCCTGCTGCGCACGTGGGAAGCCCTGGCCCC
GGCCACCCCCGCGATGCCGCGCGCTCCCCGCTGCCGAGCCGTGCGCTCCCTGCT
GCGCAGCCACTACCGCGAGGTGCTGCCGCTGGCCACGTTCGTGCGGCGCCTGGG
GCCCCAGGGCTGGCGGCTGGTGCAGCGCGGGGACCCGGCGGCTTTCGCGCGCT
GGTGGCCCAGTGCCTGGTGTGCGTGCCCTGGGACGCACGGCCGCCCCCGCCGC
CCCCCTCCTTCCGCCAGGTGTCCTGCCTGAAGGAGCTGGTGGCCCGAGTGCTGCA
GAGGCTGTGCGAGCGCGGCGCGAAGAACGTGCTGGCCTTCGGCTTCGCGCTGCT
GGACGGGGCCCGCGGGGGCCCCCCCCGAGGCCTTCACCACCAGCGTGCGCAGCTA
CCTGCCCAACACGGTGACCGACGCACTGCGGGGGAGCGGGGCGTGGGGGCTGCT
GCTGCGCCGCGTGGGGEGACGACGTGCTGGTTACCTGCTGGCACGCTGCGCGCT
CTTTGTGCTGGTGGCTCCCAGCTGCGCCTACCAGGTGTGCGGGCCGCGCTGTA
CCAGCTCGGCGCTGCCACTCAGGCCCGGCCCCCGCCACACGCTAGTGGACCCCG
AAGGCGTCTGGGATGCGAACGGGCCTGGAACCATAGCGTCAGGGAGGCCGGGGT
CCCCCTGGGCCTGCCAGCCCCGGGTGCGAGGAGGCGCGGGGGCAGTGCCAGCCG
AAGTCTGCCGTTGCCCAAGAGGCCCAGGCGTGCGCTGCCCCCTGAGCCGGAGCG
GACGCCCCGTTGGGCAGGGGTCTTGGGCCACCCGGGCAGGACGCGTGGAACGAG
TGACCGTGGTTCCTGTGTGGTGTACCTGCCAGACCCGCCGAAGAAGCCACCTC
TTTGAGGGTGCGCTCTCTGGCACGCGCCACTCCCACCCATCCGTGGGCGCCA
GCACCACGCGGGCCCCCATCCACATCGCGGCCACCACGTCCCTGGGACACGCC
TTGTCCCCCGGTGTACGCCGAGACCAAGCACTTCCTCTACTCCTCAGGCGACAA

33 / 46

FIG.8B

GGAGCAGCTGCGGCCCTCCTTCCCTACTCAGCTCTCTGAGGCCAGCCTGACTGG
CGCTCGGAGGCTCGTGGAGACCATCTTTCTGGGTTCAGGCCCTGGATGCCAGG
GACTCCCCGCAGGTTGCCCCGCCTGCCCCAGCGCTACTGGCAAATGCGGCCCT
GTTTCTGGAGCTGCTTGGGAACCACGCGCAGTGCCCCTACGGGGTGCTCCTCAA
GACGCACTGCCCGCTGCGAGCTGCGGTACCCCCAGCAGCCGGTGTCTGTGCCCG
GGAGAAGCCCCAGGGCTCTGTGGCGGCCCCCGAGGAGGAGGACACAGACCCCCG
TCGCCTGGTGCAGCTGCTCCGCCAGCACAGCAGCCCCTGGCAGGTGTACGGCTT
CGTGCGGGCCTGCCTGCGCCGGCTGGTGCCCCCAGGCCTCTGGGGCTCCAGGCA
CAACGAACGCCGCTTCCTCAGGAACACCAAGAAGTTCATCTCCCTGGGGAAGCA
TGCCAAGCTCTCGCTGCAGGAGCTGACGTGGAAGATGAGCGTGCGGGACTGCGC
TTGGCTGCGCAGGAGCCCAGGGGTGGCTGTGTTCCGGCCGCAGAGCACCGTCT
GCGTGAGGAGATCCTGGCCAAGTTCCTGCACTGGCTGATGAGTGTGTACGTCT
CGAGCTGCTCAGGTCTTTCTTTTATGTCACGGAGACCACGTTTCAAAGAACAG
GCTCTTTTCTACCGGAAGAGTGTCTGGAGCAAGTTGCAAAGCATTGGAATCAG
ACAGCACTTGAAGAGGGTGCAGCTGCGGGAGCTGTCGGAAGCAGAGGTCAGGCA
GCATCGGGAAGCCAGGCCCGCCCTGCTGACGTCCAGACTCCGCTTCATCCCCAA
GCCTGACGGGCTGCGGCCGATTGTGAACATGGACTACGTCTGTTGGAGCCAGAAC
GTTCCGCAGAGAAAAGAGGGCCGAGCGTCTCACCTCGAGGGTGAAGGCACTGTT
CAGCGTGCTCAACTACGAGCGGGCGCGGCCCGCCCTCCTGGGCGCCTCTGT
GCTGGGCCTGGACGATATCCACAGGGCCTGGCGCACCTTCGTGCTGCGTGTGCG

34 / 40

FIG.8C

GGCCCAGGACCCGCCGCTGAGCTGTACTTTGTCAAGGTGGATGTGACGGGCGC
GTACGACACCATCCCCAGGACAGGCTCACGGAGGTCATCGCCAGCATCATCAA
ACCCAGAACACGTACTGCGTGCGTCGGTATGCCGTGGTCCAGAAGGCCGCCCA
TGGGCACGTCCGCAAGGCCTTCAAGAGCCACGTCTCTACCTTGACAGACCTCCA
GCCGTACATGCGACAGTTCGTGGCTCACCTGCAGGAGACCAGCCCGCTGAGGGA
TGCCGTCGTTCATCGAGCAGAGCTCCTCCCTGAATGAGGCCAGCAGTGGCCTCTT
CGACGTCTTCCTACGCTTCATGTGCCACCACGCCGTGCGCATCAGGGGCAAGTC
CTACGTCCAGTGCCAGGGGATCCCGCAGGGCTCCATCCTCTCCACGCTGCTCTG
CAGCCTGTGCTACGGCGACATGGAGAACAAAGCTGTTTGCGGGGATTTCGGCGGGA
CGGGCTGCTCCTGCGTTTGGTGGATGATTTCTTGTTGGTGACACCTCACCTCAC
CCACGCGAAACCTTCCTCAGGACCCTGGTCCGAGGTGTCCCTGAGTATGGCTG
CGTGGTGAACCTTGCGGAAGACAGTGGTGAACCTTCCCTGTAGAAGACGAGGCCCT
GGGTGGCACGGCTTTTGTTTCAGATGCCGGCCACGGCCTATTCCCCTGGTGCGG
CCTGCTGCTGGATAACCGGACCCTGGAGGTGCAGAGCGACTACTCCAGCTATGC
CCGGACCTCCATCAGAGCCAGTCTCACCTTCAACCGCGGCTTCAAGGCTGGGAG
GAACATGCGTCGCAAACTCTTTGGGGTCTTGCGGCTGAAGTGTCACAGCCTGTT
TCTGGATTTGCAGGTGAACAGCCTCCAGACGGTGTGCACCAACATCTACAAGAT
CCTCCTGCTGCAGGCGTACAGGTTTCACGCATGTGTGCTGCAGCTCCCATTTC
TCAGCAAGTTTGGAAGAACCCACATTTTCTCCTGCGCGTCATCTCTGACACGGC
CTCCCTCTGCTACTCCATCCTGAAAGCCAAGAACGCAGGGATGTCGCTGGGGGC

35 / 40

FIG.8D

CAAGGGCGCCGCGCCGGCCCTCTGCCCTCCGAGGCCGTGCAGTGGCTGTGCCACCA
AGCATTCCTGCTCAAGCTGACTCGACACCGTGTACCTACGTGCCACTCCTGGG
GTCCTCAGGACAGCCCAGACGCAGCTGAGTCGGAAGCTCCCGGGGACGACGCT
GACTGCCCTGGAGGCCGCAGCCAACCCGGCACTGCCCTCAGACTTCAAGACCAT
CCTGGACTGATGGCCACCCGCCCACAGCCAGGCCGAGAGCAGACACCAGCAGCC
CTGTCACGCCGGGCTCTACGTCCCAGGGAGGGAGGGCGGCCACACCCAGGCC
CGCACCGCTGGGAGTCTGAGGCCTGAGTGAGTGTTTGGCCGAGGCCTGCATGTC
CGGCTGAAGGCTGAGTGTCGGCTGAGGCCTGAGCGAGTGTCCAGCCAAGGGCT
GAGTGTCAGCACACCTGCCGTCTTCACTTCCCCACAGGCTGGCGCTCGGCTCC
ACCCAGGGCCAGCTTTTCCTCACCAGGAGCCCGGCTTCCACTCCCCACATAGG
AATAGTCCATCCCCTGAT

36 / 46

FIG.9A

HASGQRCVLLRTWEALAPATPAMPRAPRCRAVRSLLRSHYREVLPLATF
VRLGPGQWRLVQRGDPAAFRALVAQCLVCVPWDARPPPAAPSFRQVSC
LKELVARVLQRLCERGAKNVLAFGFALLDGARGGPPEAFTTSVRSYLPN
TVTDALRGSGAWGLLLRRVGDDVLVHLLARCALFVLVAPSCAYQVCGPP
LYQLGAATQARPPPHASGPRRRLGCERAWNHSVREAGVPLGLPAPGARR
RGSASRSLPLPKRPRRGAAPEPERTPVGQGSWAHPGRTRGPSDRGFCV
VSPARPAEEATSLEGALSGTRHSHPSVGRQHHAGPPSTSRPPRPWDTPC
PPVYAETKHFLYSSGDKEQLRPSFLLSSLRPSLTGARRLVETIFLGSRP
WMPGTPRRLPRLPQRYWQMRPLFLELLGNHAQCPYGVLLKTHCPLRAAV
TPAAGVCAREKPQGSVAAPEEEDTDPRLVQLLRQHSSPWQVYGFVRAC
LRLRVPPGLWGSRHNERFLRNTKKFISLGKHAKLSLQELTWKMSVRDC
AWLRRSPGVGCVPAAEHRLREEILAKFLHWLMSVYVVELLRSFFYVTET
TFQKNRLFFYRKSVWSKLQSIGIRQHLKRVQLRELSEAEVRQHREARPA
LLTSRLRFIPKPDGLRPIVNMDYVVGARTFRREKRAERLTSRVKALFSV
LNYERARRPGLLGASVLGLDDIHRAWRTFVLRVRAQDPPPELYFVKVDV
TGAYDTIPQDRLTEVIASIIKPQNTYCVRRYAVVQKAAHGHVRKAFKSH
VSTLTDLQPYMRQFVAHLQETSPLRDAVVIEQSSSLNEASSGLFDVFLR
FMCHHAVRIRGKSYVQCQGIPOGSILSTLLCSLCYGD MENKLFAGIRRD
GLLLRLVDDFLLVTPHLTHAKTFLRTLVRGVPEYGCVVNLRKTVVNFV

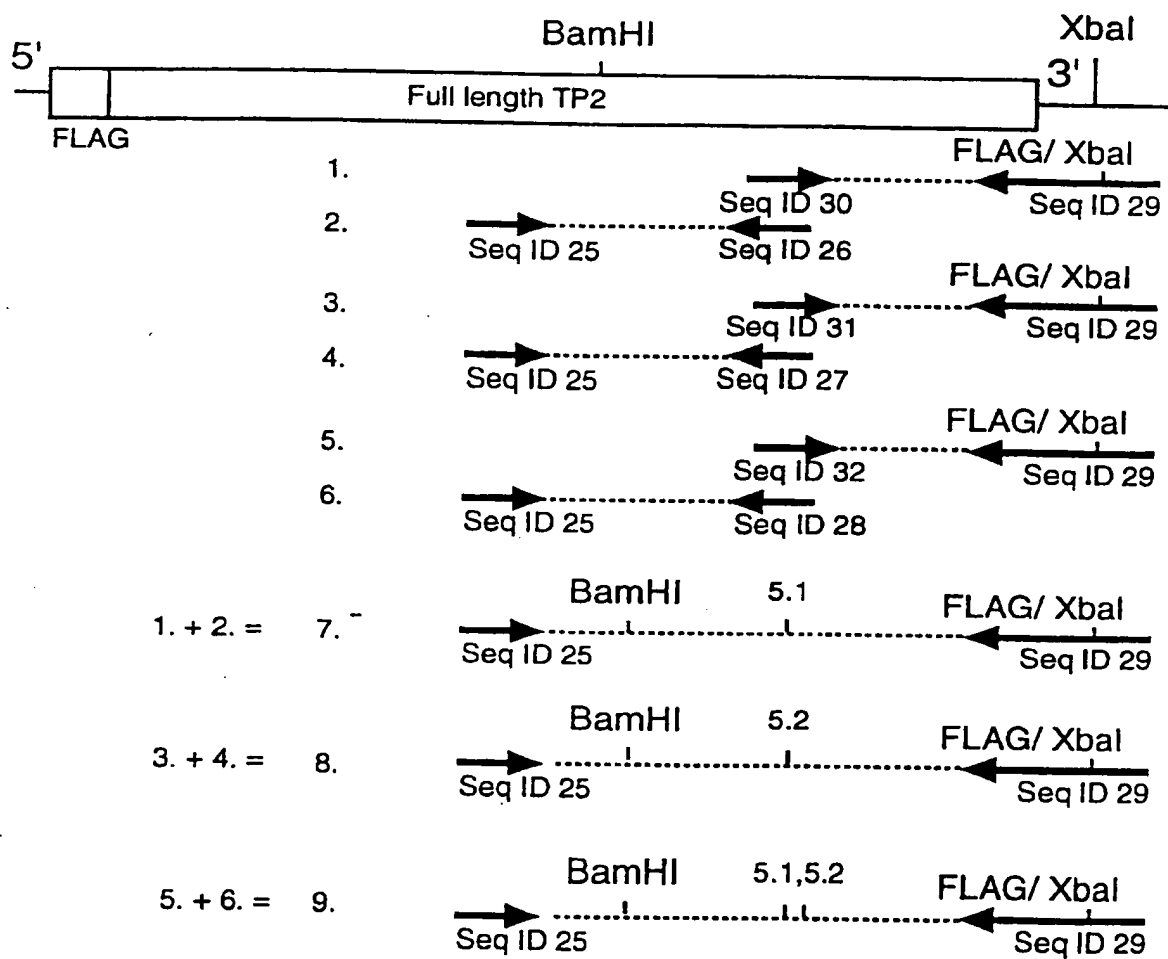
37 / 46

FIG.9B

EDEALGGTAFVQMPAHGLFPWCGLLLDTRTLEVQSDYSSYARTSIRASL
TFNRGFKAGRNMRRKLFGLRLKCHSLFLDLQVNSLQTVCTNIYKILLL
QAYRFHACVLQLPFHQVWKNPTFFLRVISDTASLCYSILKAKNAGMSL
GAKGAAGPLPSEAVQWLCHQAFLLKLTRHRVTYVPLLGSLRTAQTQLSR
KLPGTTLTALEAAANPALPSDFKTILD

38 / 46

FIG. 10



WO 98/21343

PCT/US97/21248

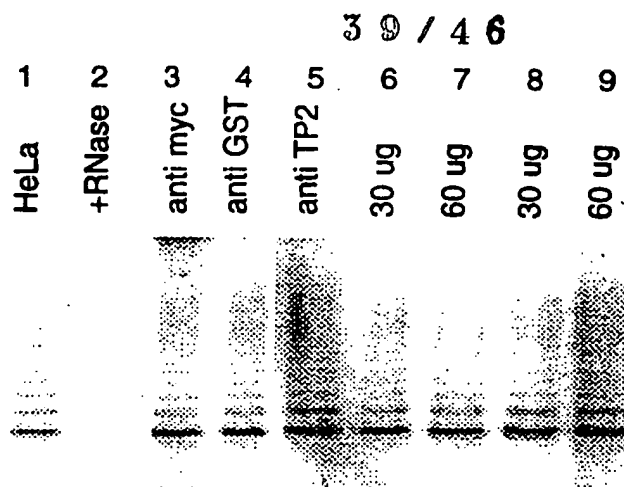


FIG. 11A

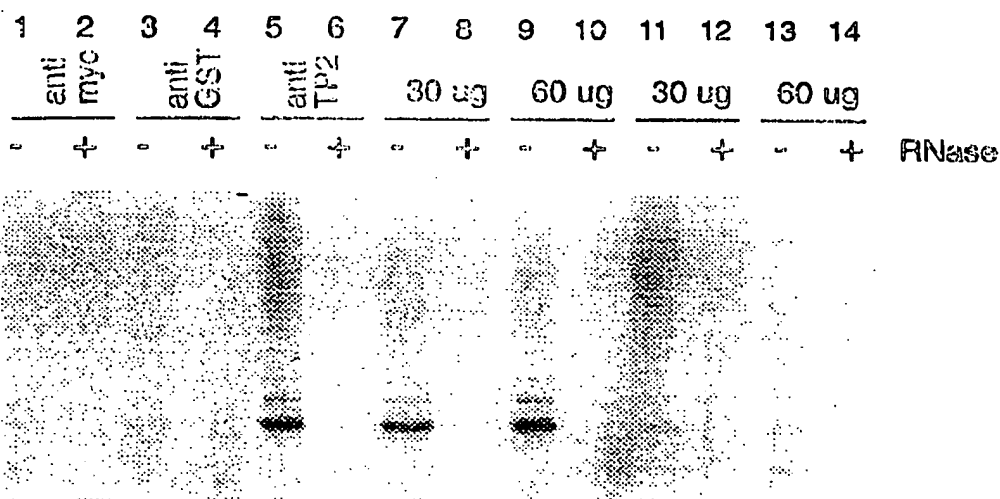


FIG. 11B

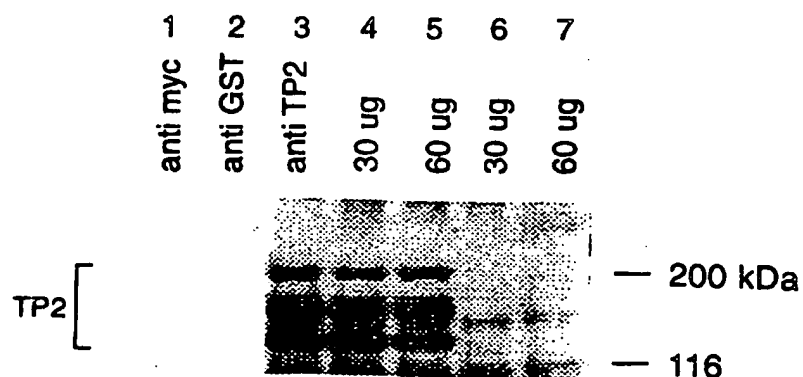


FIG. 11C

WO 98/21343

PCT/US97/21248 -

40 / 46

Mock					WT		5-1		5-1.2		5-2							
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
					-	+	-	+	-	+	-	+	-	+	-	+	-	+
					Mock		WT - PEP		WT + PEP		WT + NS PEP		5-1		5-1.2		5-2	
					RNase													



FIG. 12A

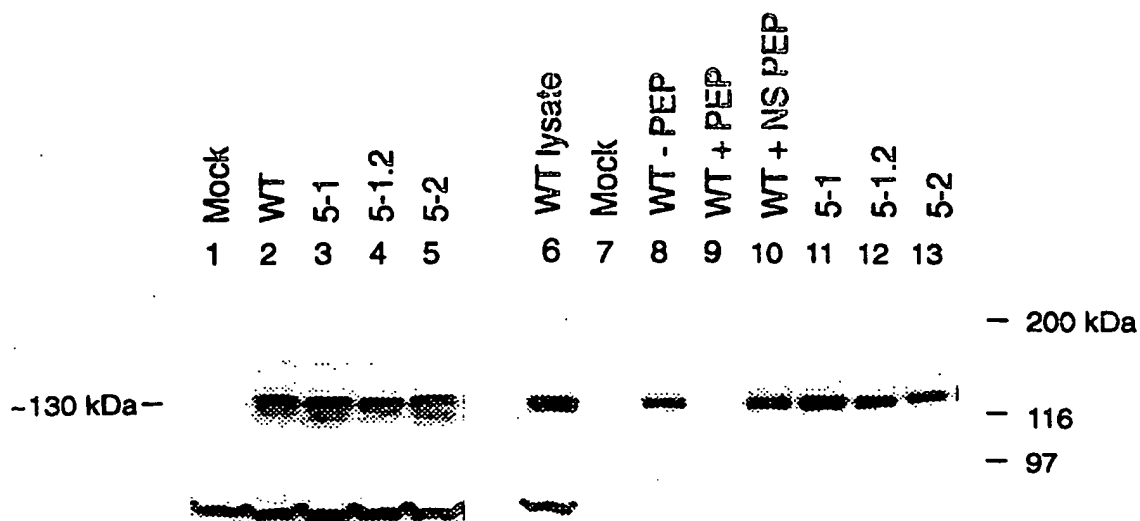


FIG. 12B

41 / 46

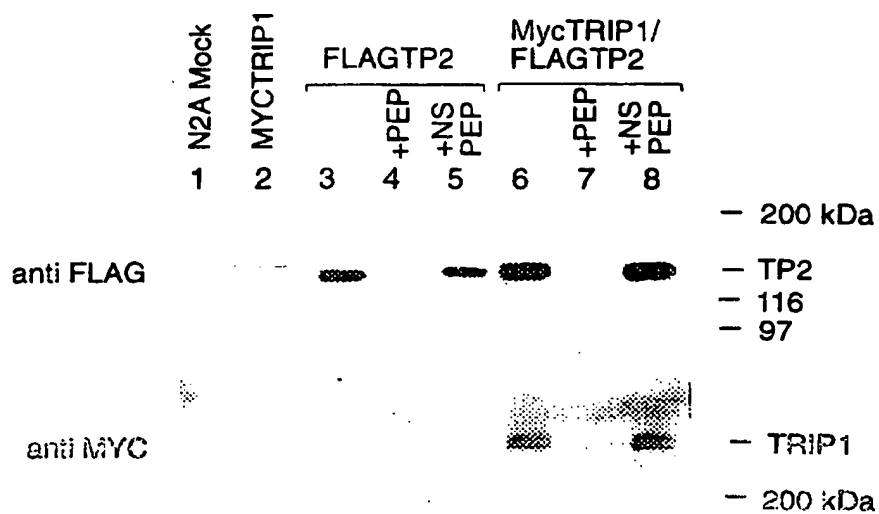


FIG.13A

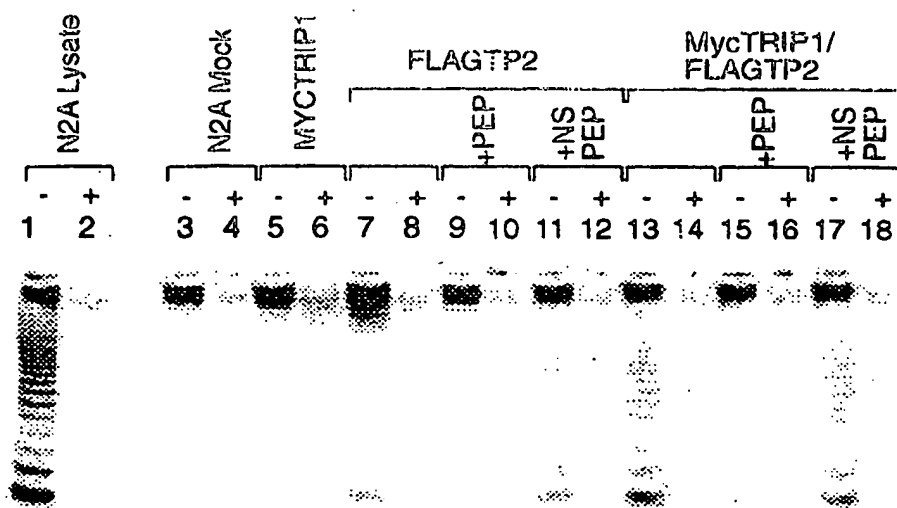


FIG.13B

WO 98/21343

PCT/US97/21248

42 / 46

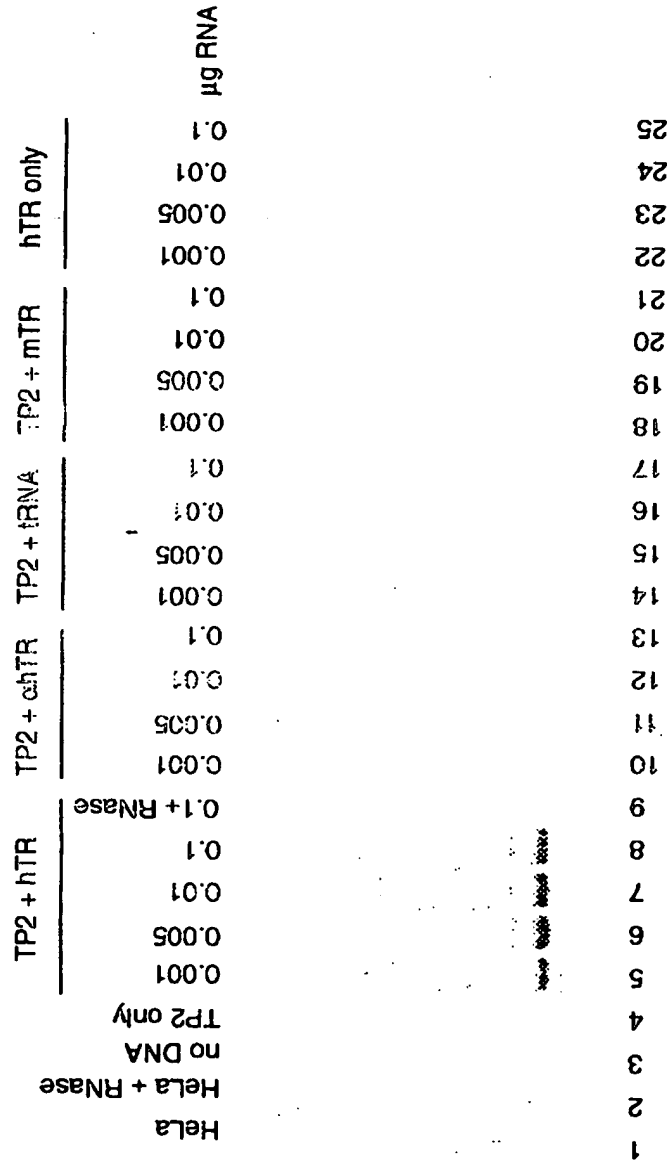


FIG. 14

WO 98/21343

PCT/US97/21248 -

43 / 46

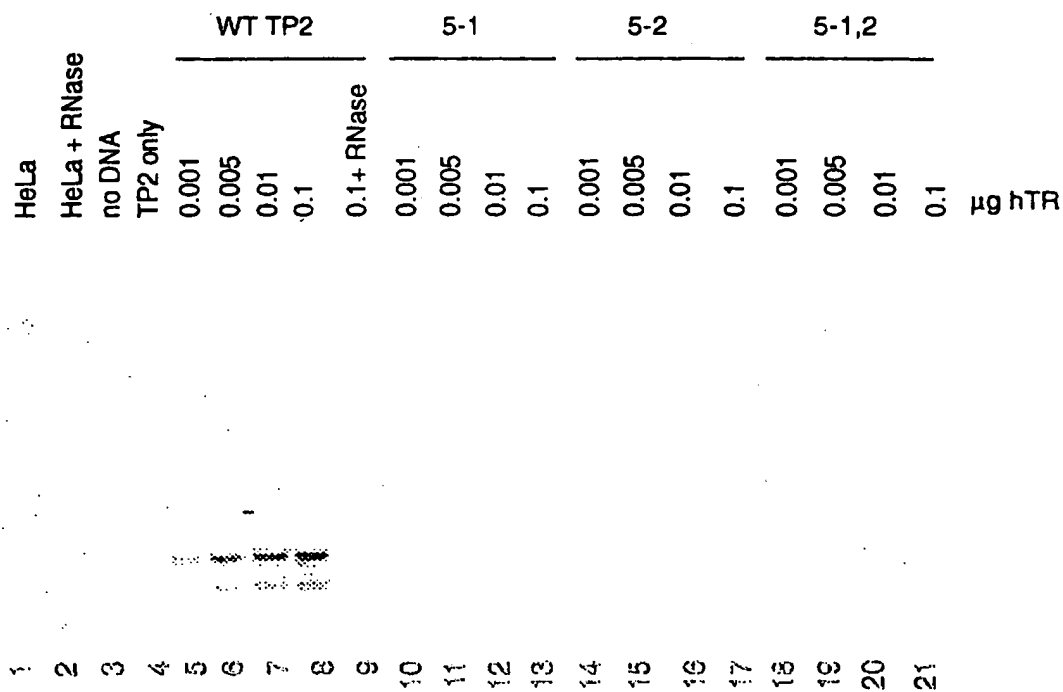


FIG. 15A

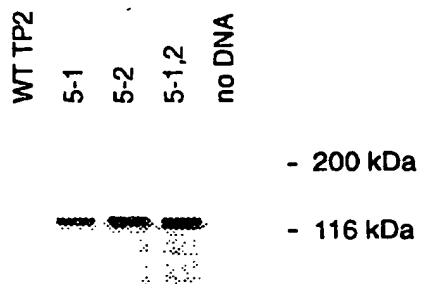


FIG. 15B

WO 98/21343

PCT/US97/21248

44 / 46

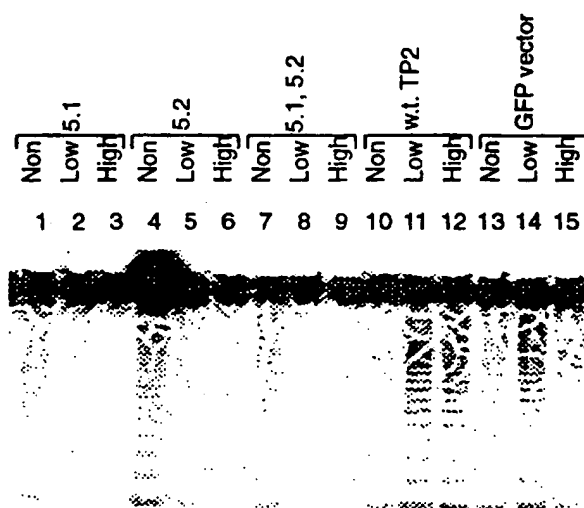


FIG. 16A

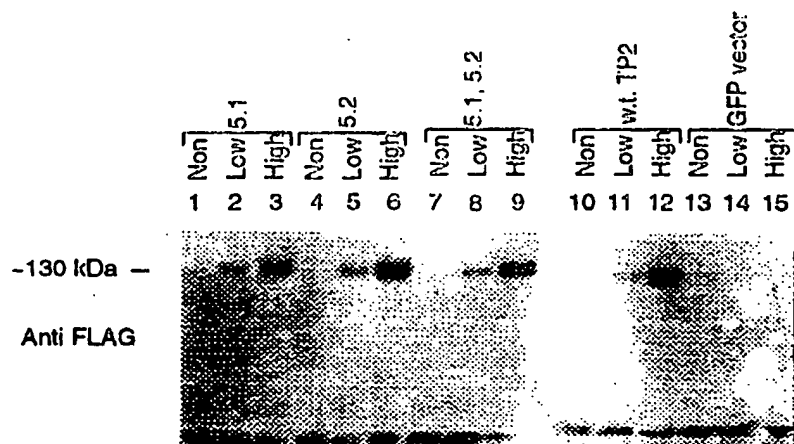


FIG. 16B

WO 98/21343

PCT/US97/21248

45 / 46

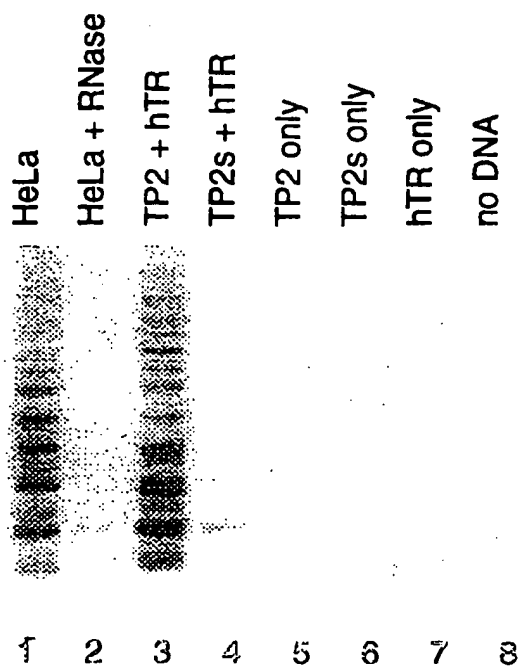


FIG. 17A

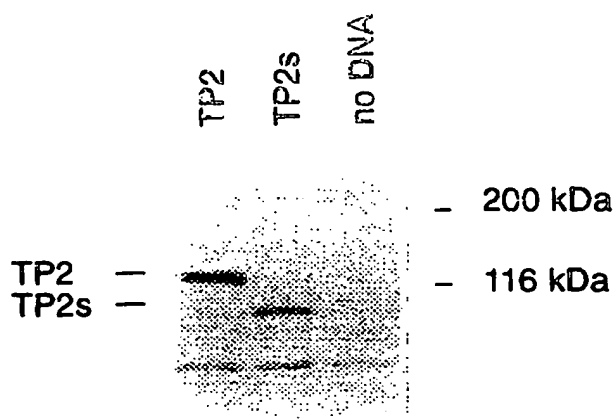


FIG. 17B

WO 98/21343

PCT/US97/21248 -

46 / 46

no DNA		TP2+hTR				μ L assayed
		-TP1		+ TP1		
1	2	1	2	1	2	

1 2 3 4 5 6

FIG.18